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10/031,660	01/16/2002	Henry Yue	PF-0714 USN	4258

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,660	YUE ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1,2,9, 10 and 13-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-8,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 72 (claims 3-8, 11 and 12, SEQ ID NO: 72) in the reply filed on May 14, 2004 is acknowledged. The traversal is on the ground(s) that can be summarized as follows:

A) the unity of invention standard ***must*** be applied in national stage application, therefore the examiner is **required** to apply the unity of invention standard (Applicants' emphasis), therefore, proteins and nucleic acids encoding them should be examined together,

B) unity of invention exists among all Applicants' claims, because the sequences of claimed polypeptides and polynucleotides encoding these polypeptides are the corresponding technical features which are common to all claims,

C) the examiner's reasoning supporting the lack of unity is incorrect in that, as stated by Applicants, "that is those polypeptide sequences and/or those corresponding polynucleotide sequences in their **entire** form which provide the "common or corresponding special technical feature" linking all of the claims to form a single general inventive concept.". The Applicants further argue that it is the full-length sequences of claims 1 and 5 are not disclosed by any fragments of theses sequences, "...therefore the contribution over the prior art represented by the full-length polypeptide and polynucleotide sequences is not negated by such fragments."

This is not found persuasive because, to go directly to the crucial point, claim 1 is a Markush claim having four parts: a), drawn to amino acid sequences selected from the group consisting of SEQ ID NO: 1-SEQ ID NO: 66, part b), drawn to amino acid sequences having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO: 1-SEQ ID NO: 66, part c), drawn to a biologically active fragment of an amino acid sequence selected

from the group consisting of SEQ ID NO: 1-SEQ ID NO: 66, and part d), drawn to an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO: 1-SEQ ID NO: 66. Therefore, either of the parts can be considered as a "special technical feature" of claim 1, since they are all independent of each other, and art against any of the parts a)-d) would lead to the rejection of the claim. Further, claim 2 is drawn to polynucleotides encoding polypeptides of claim 1, therefore, also to polynucleotides encoding not only full-length sequences of claim 1 a), but also fragments of claims 1 c) and 1 d). Thus, the full-length polypeptide sequences of claim 1 are not the only ones which can be considered as a "special technical feature" presented by the claim. Since a prior art sequence with Accession No. Q05473 discloses fragments of SEQ ID NO: 1, and fragments of SEQ ID NO: 1 can be considered as a special technical feature, therefore, since that special technical feature is disclosed in the prior art, there is no lack of unity in the invention. In other words, there is no contribution of the special technical feature of claim 1 over the prior art, therefore there is no lack of unity of the invention.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1, 2, 9, 10 and 13-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 14, 2004.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claims 3-8, 11 and 12 will be considered to the degree that they read on polynucleotide with SEQ ID NO: 72 or a sequence encoding a polypeptide with SEQ ID NO: 6.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on May 14, 2004 was filed after the mailing date of the Restriction/Election Requirement on April 19, 2004. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 3- 8, 11 and 12 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a an isolated polynucleotide consisting of SEQ ID NO: 72, an isolated polynucleotide comprising a naturally occurring polynucleotide having at least 70% sequence identity to SEQ ID NO: 72, or an isolated polynucleotide comprising at least 60 contiguous nucleotides of either SEQ ID NO: 72, as well as to a polynucleotide encoding an isolated polypeptide of SEQ ID NO: 6, a polynucleotide encoding a polypeptide with 90% sequence identity to SEQ ID NO: 6, a polynucleotide encoding a biologically active fragment of a polypeptide of SEQ ID NO: 6 and a polynucleotide encoding an immunogenic fragment of SEQ ID NO: 6.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21,

1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the nucleic acids. The only cited utilities identified by the examiner are production of transgenic animals and cells (page 35, lines 24-36; page 36, lines 1-16), antisense molecules (page 41, lines 14-32), gene therapy (page 41, lines 33-35; page 42-44), screening for compounds which alter gene expression (page 46, lines 8-35), as hybridization probes (page 49, lines 25-35; page 50, lines 1-13; page 54, lines 2-16; page 57, lines 7-35), for diagnosis of disorders associated with expression of GTP-binding associated proteins (GBAPs) (page 50, lines 14-35; page 51, 52), as primers (page 53, lines 5-11), to detect SNPs (page 53, lines 12-29) and in analysis of gene expression (page 54, lines 17-35). These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the nucleic acid comprising SEQ ID NO: 72. No well established utilities for this specific nucleic acid are identified in the specification.

Substantial utility

Given the absence of a well established utility, the next issue is whether substantial utilities are disclosed in the specification. As provided by the specification, nucleic acid with SEQ ID NO: 72 has been cloned from a breast tissue removed from a 67-year old woman during mastectomy (Table 4, page 100). The level of expression of SEQ ID NO: 72 in different tissues has been determined by an "in silico" Northern blot against sequences from a range of libraries. The results are classified in terms of "expression" detected in different types of tissues in Table 3 (page 94). SEQ ID NO: 72 seems to be expressed in gastrointestinal, reproductive and cardiovascular tissues, as well as in "disease" tissues such as cancer, cell proliferation and inflammation/trauma. There is no other information about the expression levels of SEQ ID NO: 72. Applicants have not provided

a description of the libraries against which the "screening" was performed, therefore, both the "tissue" and the "disease" tissue categories are totally uninformative, since they include possibly a lot of different types of tissues at different stages of maturation, disease progression levels, etc. In summary, the data on expression of SEQ ID NO: 72 in "cancer" does not allow for establishing whether the "expression level" determined computationally has any meaning.

For example, let us assume that the "cancer" tissue was from a breast cancer. To be able to determine whether SEQ ID NO: 72 is related in any way to breast cancer, one would need to know the level of expression of SEQ ID NO: 72 in normal breast tissue for comparison. This information is lacking.

As noted in the utility guidelines, methods of treating unspecified diseases, basic research on a product to identify properties, intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials). In the instant case, additional research would be necessary to establish substantial utility of a nucleic acid comprising SEQ ID NO: 72. On pages 36-38 and 50-52 Applicants provided a laundry lists of disorders which might be associated with the polynucleotides of the invention. This list encompasses practically all possible disorders afflicting humankind, without providing any relationship to the polynucleotides or polypeptides of the invention, and to SEQ ID NO: 72 in particular.

In order for a polynucleotide to be useful for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in some type of tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polynucleotide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be

identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

In addition, since the specification has failed to establish a relationship between the polynucleotide of SEQ ID NO: 72 or its fragments and any specific disease or establish any involvement of the polynucleotide of SEQ ID NO: 72 in the etiology of any specific disease, a cell expressing the polynucleotide of SEQ ID NO: 72 would not have any substantial utility, since the effects of the polynucleotide expression cannot be predicted. Further, a transgenic animal comprising a cell that comprises a polynucleotide of SEQ ID NO: 72 would have not any apparent or predictable phenotype since the function of the protein encoded by this polynucleotide is unknown. In the absence of any apparent phenotype, a transgenic animal would have no obvious utility that is substantial.

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, then the specific utility of the polynucleotide consisting of SEQ ID NO: 72 is, at best, a relationship to an association with an undefined "cancer" tissue. This utility is not specific because there are a lot of different nucleic acids expressed in different "cancer" tissues, 67 of them provided by Applicants. Thus, the presence of the nucleic acids in an unspecified "cancer" tissue does not provide a specific utility because there is no direct or even indirect connection made between any particular utility and the polynucleotide consisting of SEQ ID NO: 72. Therefore, even though Applicants claim that the nucleic acids could be used in detection and monitoring of a large number of diseases, no specific association between these diseases and SEQ ID NO: 72 has been provided, and thus, no specific utility for SEQ ID NO: 72. Since there is no specific utility for a polynucleotide of SEQ ID NO: 72, a cell comprising the polynucleotide and a transgenic animal comprising a cell have no specific utility for reasons discussed above.

Claim Rejections - 35 USC § 112, written description

8. Claims 3, 6-8, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 3 is drawn to a an isolated polynucleotide encoding an isolated polypeptide consisting of SEQ ID NO: 6, encoding polypeptides with sequences having at least 90% identity to SEQ ID NO: 6, or encoding biologically active fragments or immunogenic fragments of SEQ ID NO: 6. Claim 6 is drawn to a polynucleotide comprising a promoter sequence linked to a polynucleotide of claim 3, claim 7 is drawn to a cell transformed with a recombinant polynucleotide of claim 6 and

claim 8 is drawn to a transgenic organism comprising a recombinant polynucleotide of claim 6. Claim 11 is drawn to an isolated polynucleotide comprising a naturally occurring polynucleotide having at least 70% sequence identity to SEQ ID NO: 72, a polynucleotide sequence complementary to an isolated polynucleotide comprising a naturally occurring polynucleotide having at least 70% sequence identity to SEQ ID NO: 72 and RNA equivalents of the latter two sequences, and claim 12 is drawn an isolated polynucleotide comprising at least 60 contiguous nucleotides of either SEQ ID NO: 72 or an isolated polynucleotide comprising a naturally occurring polynucleotide having at least 70% sequence identity to SEQ ID NO: 72, their complements and RNA equivalents.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification, such as all possible sequences with 70% identity to SEQ ID NO: 72 or all possible polynucleotides comprising at least 60 contiguous nucleotides of SEQ ID NO: 72. In the latter case all that is required is 60 bp identical to SEQ ID NO: 72, and all the rest of the sequence can be any sequence whatsoever, providing for millions of possible polynucleotides. Further, a limitation of a polynucleotide comprising at least 60 contiguous nucleotides of a sequence

70% identical to SEQ ID NO: 72 results in any sequence, since the contiguous 60 bp may be outside of the region of homology with SEQ ID NO: 72, again, providing for millions of possible sequences. This large genus is represented in the specification by only the particularly named SEQ ID No: 72. Thus, applicant has express possession of only one particular nucleic acid, in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these limitations is provided. No written description of alleles, of upstream or downstream regions containing additional sequence has been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the polynucleotide encoding a biologically active fragment of SEQ ID NO: 6 lack any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for one specific SEQ ID NO: 72, is in the absence of knowledge of the material composition and fails to provide descriptive support for

the generic claim to "polynucleotide encoding a biologically active fragment of SEQ ID NO: 6", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, one specific SEQ ID NO is described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which consist of SEQ ID NO: 72. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 112, enablement

9. Claims 3-8, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Nature of the Invention and Breadth of Claims

The current claims are drawn to a an isolated polynucleotide consisting of SEQ ID NO: 72, an isolated polynucleotide comprising a naturally occurring polynucleotide having at least 70% sequence identity to SEQ ID NO: 72, or an isolated polynucleotide comprising at least 60 contiguous nucleotides of either SEQ ID NO: 72, as well as to a polynucleotide encoding an isolated polypeptide of SEQ ID NO: 6, a polynucleotide encoding a polypeptide with 90% sequence identity to SEQ ID NO: 6, a polynucleotide encoding a biologically active fragment of a polypeptide of SEQ ID NO: 6 and a polynucleotide encoding an immunogenic fragment of SEQ ID NO: 6. The specification does not provide any utility for the claimed polynucleotides. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Unpredictability of the Art and the State of the Prior Art

In the current case, where no specific information is known regarding the function of the polynucleotide in actual biological organisms, it is entirely unpredictable what function will be found for this polynucleotide. The prior art does not resolve this ambiguity, since no prior art activity is identified for the polynucleotide.

Applicants have not provided any information about the function of polynucleotide of SEQ

ID NO: 72. No convincing information was provided as to the link of the polynucleotide of SEQ ID NO: 2 to any specific disease or group of diseases. In the specification Applicants contemplate using the polynucleotide of SEQ ID NO: 72 to produce transgenic animals or for gene therapy, for example.

As to the transgenic animals, the result of inserting a polynucleotide of SEQ ID NO: 72 into such animal would produce entirely unpredicatabe result, since such transgenic animal would not have any apparent or predictable phenotype since the function of the protein encoded by this polynucleotide is unknown. In the absence of any apparent phenotype, a transgenic animal would not be of any use. The specification has contemplated that embryonic stem (ES) cells may be used to create transgenic animals (see page 35, lines 24-36; page 36, lines 1-16). Currently, the state of the transgenic art regarding ES cell technology for the production of transgenic animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system and that only putative ES cells exist for other species. See Moreadith et al. (J. Mol. Med., vol. 75, pp. 208-216, 1997, Summary, page 214). Mullins et al. (Journal of Clinical Investigation, vol. 98, pp. S37-S40, 1996) state that "although to date chimeric animals have been generated from several species includingthe pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page 538, column 1, first paragraph). The state of the art does not support the use of embryonic stem cells for creating knockout rats or other animals. Given the unpredictable and undeveloped state of the ES cells art it would have required undue experimentation for the skilled artisan to create transgenic knockout of organisms other than mouse.

In terms of application of polynucleotide of SEQ ID NO: 72 to gene therapy, the lack of association of this polynucleotide with any disease would lead to unpredictable results upon its administration. Further, gene therapy for either non-malignant diseases or cancer is not an

established treatment modality, fraught with low success rate, unpredictable results and side effects. In a recent review of gene therapy trials for non-malignant diseases, Ratko et al. (Am. J. Med., vol. 115, pp. 560-569) note that all of the gene transfer vector systems have disadvantages (Table 1), limited success of gene therapies for cystic fibrosis and hemophilia (page 563, paragraphs 2-4), inconclusive results for using VGEF gene transfer in coronary artery disease. The authors summarize the paper in the following statement (page 566, second paragraph):

> "... Despite its promise, gene therapy is not yet sufficiently developed for clinical use for several reasons. First, the quantity of transgene product needed to relieve or reverse illness is unknown. Transgene overexpression or underexpression could pose unforeseen dangers to the patient, with unpredictable outcomes. The optimal dose of vector and its passenger gene necessary to achieve a beneficial therapeutic outcome with an adequate margin of safety has not been established. Second, the specificity of transgene delivery is critical to the success of gene therapy, yet this issue remains probably the most important barrier to success. Direct and indirect routes of transgene administration have been investigated, with some signs of success but no clear-cut evidence of efficacy in any disease. Third, the control of transgene expression within target cells at physiologically regulated levels for appropriate periods of time is problematic."

De Giovanni et al. (In. J. Immunopharmacol., vol. 22, pp. 1025-1032, 2000) review cancer gene therapy, concluding that gene therapy had very limited success in inhibiting cancer, and that different approaches to cancer gene therapy all have different types of problems (Abstract; page 1026, paragraphs 2-5; page 1029, paragraphs 4 and 5). No efficacy has been shown for metastatic disease, for example (page 1031, third paragraph).

Therefore, id addition to uncertain function of the polynucleotide with SEQ ID NO: 72, which would make its use in gene therapy unpredictable, the gene therapy itself is still an unpredictable art.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the function of nucleic acids, which depends on their sequence and origins. It would require significant study to identify the actual function of the polynucleotide with SEQ ID NO: 72, and identifying a use for this polynucleotide would be an inventive, unpredictable and difficult undertaking in itself. Applicants assert that the polynucleotide with SEQ ID NO: 72 could be used to diagnose or treat a disorder associated with a an altered expression of the polynucleotide, and listed two pages of such disorders, some of which correspond to general categories of disorders, such as cancer. However, the polynucleotide of SEQ ID NO: 72 has not been associated with any one of these disorders. Therefore, one of ordinary skill in the art would have to perform more than routine experimentation to determine the function of this polynucleotide and its association with any of the listed disorders, as well as to determine whether the presence of this polynucleotide is indeed indicative of any of the disorders and can be used for diagnostic purposes. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Further, use of the polynucleotides which are 70% homologous to SEQ ID NO: 72 or polynucleotides comprising at least 60 contiguous nucleotides of SEQ ID NO: 72 is even more problematic, since these polynucleotides may have very different functions from the polynucleotide of SEQ ID NO: 72.

The Amount of Direction or Guidance Presented

As provided by the specification, nucleic acid with SEQ ID NO: 72 has been cloned from a breast tissue removed from a 67-year old woman during mastectomy (Table 4, page 100). The level of expression of SEQ ID NO: 72 in different tissues has been determined by an "in silico" Northern blot against sequences from a range of libraries. The results are classified in terms of "expression"

detected in different types of tissues in Table 3 (page 94). SEQ ID NO: 72 seems to be expressed in gastrointestinal, reproductive and cardiovascular tissues, as well as in "disease" tissues such as cancer, cell proliferation and inflammation/trauma. There is no other information about the expression levels of SEQ ID NO: 72. Applicants have not provided a description of the libraries against which the "screening" was performed, therefore, both the "tissue" and the "disease" tissue categories are totally uninformative, since they include possibly a lot of different types of tissues at different stages of maturation, disease progression levels, etc. In summary, the data on expression of SEQ ID NO: 72 in "cancer" does not allow for establishing whether the "expression level" determined computationally has any meaning. Therefore, there is no correlation that can be made between a polynucleotide with SEQ ID NO: 72 and detection of any particular cancers.

The Presence or Absence of Working Examples

No working examples for the polynucleotide of SEQ ID NO: 72 were provided.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define the variables necessary to elucidate the function of the polynucleotides, the lack of guidance provided in the specification, the absence of a working example balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to use the polynucleotides of the invention.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 3 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Brondyk et al. (Mol. Cell. Biol., vol. 15, pp. 1137-1143, 1995; cited in the IDS).

Regarding claim 3, Brondyk et al. teach a nucleic acid with accession No. U19181 which encodes a protein, Rabin3, with 90.65% sequence identity to SEQ ID NO: 6 (Fig. 1A, page 1138, 7th paragraph) (see sequence alignment). Brondyk et al. also teach biologically active fragments of the Rabin3 protein, for example, fragments with amino acids 101-460 (Fig. 5 and 6), fragments with amino acids 1-222 and 1-316 (Fig. 6). Therefore, Brondyk et al. anticipate the limitations of claim 3 by disclosing a polynucleotide encoding a polypeptide having at least 90% sequence identity to SEQ ID NO: 6 and a polynucleotide encoding active fragments of SEQ ID NO: 6.

Regarding claim 6, Brondyk et al. teach expression of Rabin3 and its fragments as a GST-fusion protein from the pGEX-2T vector in the DH5α strain of E. coli (page 1138, third paragraph). Brondyk et al. do not specifically teach the polynucleotide encoding Rabin3 operably linked to a promoter, but since the protein was expressed from a vector in E. coli cells, the presence of a promoter is inherent in the teaching of the expression vector.

Regarding claims 7 and 8, Brondyk et al. teach expression of Rabin3 and its fragments in the DH5α strain of E. coli. Therefore, Brondyk et al. teach the limitation of a cell transformed with a polynucleotide of claim 6 and a transgenic organism comprising a polynucleotide of claim 6, since, as defined by Applicants, "The transgenic organisms contemplated in accordance with the present

invention include bacteria, cyanobacteria, fungi, plants, and animals." (specification, page 22, lines 21-23).

12. Claims 3 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by a sequence with Accession No. AA846576 (March 4, 1998).

Regarding claim 12, sequence with Accession No. AA846576 comprises 629 contiguous nucleotides of SEQ ID NO: 72 (see sequence alignment), therefore, it anticipates the limitation of a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO: 72.

Regarding claim 3, the 629 bp fragment potentially encodes about a 209 amino acid fragment, therefore, it anticipates the limitations of claim 3 of encoding "biologically active" and "immunogenic" fragments of SEQ ID NO: 6, since these terms were defined in the specification in the terms of structure and function of the encoded protein, which are not known. Therefore, because of a lack of functional description of a polypeptide with SEQ ID NO: 6, any fragment of it is considered to be "biologically active" or "immunogenic".

13. No references were found teaching or suggesting claims 4, 5 and 11, but they are rejected for reasons given above. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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